C3

52. (Amended) The method of claim 43, said humanized anti-VEGF antibody comprising a heavy chain variable domain sequence of SEQ ID NO:7 and a light chain variable domain sequence of SEQ ID NO:8.

## REMARKS

I. Substitute Sequence Listing and Specification Amendment:

The substitute Sequence Listing is submitted herewith to renumber some of the sequences so that the SEQ ID Numbers match between the Sequence Listing and the specification. Specifically, the sequences previously identified in the Sequence Listing as SEQ ID NO's 101 and 102 have been renumbered as SEQ ID NO's 130 and 131. Furthermore, the specification has been amended accordingly (i.e., at page 7, line 17).

II. Claim Amendments:

Claim 48 has been canceled. Claims 47 and 49-52 have been amended. Claims 47 and 49 are amended to merely clarify the characteristics of the claimed humanized anti-VEGF antibody as having a heavy chain and a light chain, wherein the heavy chain comprises a variable domain comprising the CDRs of specific amino acid sequences. Support for the amendments can be found in the specification at, for example, page 3, line 9-18 and in the originally filed claims. Claim 50 is amended to be dependent on claim 47, wherein the light chain comprises a variable domain comprising the CDRs of specific amino acid sequences. Support for the amendment of claim 50 can be found at, for example, page 3, line 29 through page 4, line 7. Claim 51 is amended to encompass a humanized anti-VEGF antibody comprising a heavy chain variable domain of SEQ ID NO:115 and a light chain variable domain of SEQ ID NO:116. Such antibody is described at, for example, page 4, line 28 through page 5, line 5 and in Figures 10A and 10B (under "Y0317"). As such, the amendments do not add new matter.

III. Restriction Requirement:

The outstanding Office Action requires Applicants to elect a single species with respect to claims 47-52. According to the Office, claims 47-52 are directed to specific SEQ ID NO's for CDRs and for entire antibodies. Claims 43-46, 53-59 are deemed as generic.

In response to the restriction requirement, and further in light of the claim amendements, Applicants hereby elect the species encompassing antibodies having CDRs of specific sequences for further prosecution. Specifically, claims 47, 49 and 50 are readable upon the elected species. This election is made without traverse.

In the event any additional fees are due in connection with the filing of these documents, the Commissioner is authorized to charge such fees to our Deposit Account No. 07-0630.

Respectfully submitted,

GENENTECH, INC.

Date: October 28, 2002 By: _____

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 7, line 15 has been amended as follows:

Figs. 8A-E depict the double stranded nucleotide sequence (SEQ ID NO:99) for phage-display antibody vector phMB4-19-1.6 in Example 3 and the amino acid sequences encoded thereby (SEQ ID NO's 100, 130 and 131).

In the Claims:

Claim 48 has been canceled. Claims 47, 49-52 have been amended as follows:

47. (Amended) The method of claim 43, said humanized anti-VEGF antibody having a heavy chain and a light chain, wherein the heavy chain comprises a variable domain comprising the following [hypervariable region] complementarity determining region (CDR) amino acid sequences: CDRH1 ($GYX_1FTX_2YGMN$, wherein $X_1$ is T or D and $X_2$ is N or H; SEQ ID NO:128), CDRH2 (WINTYTGEPTYAADFKR; SEQ ID NO:2) and CDRH3 ($YPX_1YYGX_2SHWYFDV$, wherein $X_1$ is Y or H and $X_2$ is S or T; SEQ ID NO:129).

49. (Amended) The method of claim 47, [said humanized anti-VEGF antibody having a] wherein the heavy chain comprises a variable domain comprising the following [hypervariable region] CDR amino acid sequences: CDRH 1 (GYTFTNYGMN; SEQ ID NO: l), CDRH2 (WINTYTGEPTYAADFKR; SEQ ID NO:2) and CDRH3 (YPHYYGSSHWYFDV; SEQ ID NO:3).

50. (Amended) The method of claim 47[3], [said] wherein the light chain of the humanized anti-VEGF antibody [having a light chain] comprises a variable domain comprising the following [hypervariable region] CDR amino acid sequences: CDRL1 (SASQDISNYLN; SEQ ID NO:4), CDRL2 (FTSSLHS SEQ ID NO:5) and CDRL3 (QQYSTVPWT; SEQ ID NO:6).

51. (Amended) The method of claim 43, said humanized anti-VEGF antibody comprising [the amino acid] a heavy chain variable domain sequence of SEQ ID NO:[8]115 and a light chain variable domain sequence of SEQ ID NO:116.

52. (Amended) The method of claim 43, said humanized anti-VEGF antibody [having] comprising a heavy chain variable domain [comprising the amino acid] sequence of SEQ ID NO:7 and a light chain variable domain [comprising the amino acid] sequence of SEQ ID NO:8.

## Appendix A
## Pending Claims

43. A method for inhibiting VEGF-induced angiogenesis in a subject, comprising administering to said subject an effective amount of a humanized anti-VEGF antibody which binds human VEGF with a $K_d$ value of no more than about 1 x $10^{-8}$M.

44. The method of claim 43, wherein said humanized anti-VEGF antibody which binds human VEGF with a $K_d$ value of no more than about 1 x $10^{-9}$M.

45. The method of claim 43, wherein said subject has a tumor.

46. The method of claim 45, wherein 5mg/kg of said humanized antibody inhibits at least about 50% of tumor growth in an A673 *in vivo* tumor model.

47. (Amended) The method of claim 43, said humanized anti-VEGF antibody having a heavy chain and a light chain, wherein the heavy chain comprises a variable domain comprsing the following complementarity determining region (CDR) amino acid sequences: CDRH1 ($GYX_1FTX_2YGMN$, wherein $X_1$ is T or D and $X_2$ is N or H; SEQ ID NO: 128), CDRH2 (WINTYTGEPTYAADFKR; SEQ ID NO:2) and CDRH3 ($YPX_1YYGX_2SHWYFDV$, wherein $X_1$ is Y or H and $X_2$ is S or T; SEQ ID NO: 129).

49. (Amended) The method of claim 47, wherein the heavy chain comprises a variable domain comprising the following CDR amino acid sequences: CDRH 1 (GYTFTNYGMN; SEQ ID NO: l), CDRH2 (WINTYTGEPTYAADFKR; SEQ ID NO:2) and CDRH3 (YPHYYGSSHWYFDV; SEQ ID NO:3).

50. (Amended) The method of claim 47, wherein the light chain of the humanized anti-VEGF antibody comprises a variable domain comprising the following CDR amino acid sequences: CDRL1 (SASQDISNYLN; SEQ ID NO:4), CDRL2 (FTSSLHS SEQ ID NO:5) and CDRL3 (QQYSTVPWT; SEQ ID NO:6).

51. (Amended) The method of claim 43, said humanized anti-VEGF antibody comprising a heavy chain variable domain sequence of SEQ ID NO:115 and a light chain variable domain

sequence of SEQ ID NO:116.

52. (Amended) The method of claim 43, said humanized anti-VEGF antibody comprising a heavy chain variable domain sequence of SEQ ID NO:7 and a light chain variable domain sequence of SEQ ID NO:8.

53. The method of claim 43, wherein said humanized anti-VEGF antibody is a full length antibody.

54. The method of claim 53, wherein said humanized anit-VEGF antibody is a human IgG.

55. The method of claim 43, wherein said humanized anti-VEGF antibody is an antibody fragment.

56. The method of claim 55, wherein said humanized anti-VEGF antibody is a Fab.

57. The method of claim 43, wherein said subject has a retinal disease.

58. The method of claim 57, wherein said retinal disease is age-related macular degeneration (AMD).

59. The method of claim 58, wherein the humanized anti-VEGF antibody is administered to the subject at a dose of at least about 0.5mg/kg.